

PATENT COOPERATION TREATY

PCT


INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 14 MAR 2005

WPC PCT

Applicant's or agent's file reference TLB/P409153WO		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/GB2004/001755		International filing date (day/month/year) 26.04.2004	Priority date (day/month/year) 21.05.2003	
International Patent Classification (IPC) or national classification and IPC B01J31/24, C07C67/31, C07C231/18, C07F15/00				
Applicant PHOENIX CHEMICALS LIMITED				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input checked="" type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 19.11.2004		Date of completion of this report 11.03.2005		
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80293 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Bork, A-M Telephone No. +49 89 2399-8311		



**INTERNATIONAL PRELIMINARY REPORT
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-12 as originally filed

Claims, Numbers

1-15 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
- ☒ claims Nos. 1-15 (partly)
because:
- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-15 (partly)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|--|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	partly: 1-15
	No: Claims	
Inventive step (IS)	Yes: Claims	partly: 1-15
	No: Claims	
Industrial applicability (IA)	Yes: Claims	partly: 1-15
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III.

The following Written Opinion is based only on those part of the claims for which the Search Report was establish (Rule 66.1(e) PCT), namely

- a catalytic composition comprising a catalyst as defined in claim 2 (i.e. BINAP or other biaryl bisphosphine-based ligand catalyst) and a buffering composition comprising a mixture of a ketone/or an aldehyde and an alcohol (as defined in the description on page 4, line 27 - page 5, line 3) suitable for use in the enantioselective hydrogenation of beta-ketoesters according to claim 3;
- the process for the enantioselective catalytic hydrogenation of beta-ketoesters according to claim 10 comprising contacting a ketoester with hydrogen and with a catalyst according to claim 9 (BINAP or other biaryl bisphosphine-based ligand catalyst) in the presence of a buffering composition comprising a mixture of a ketone/or an aldehyde and an alcohol;
- use of a buffering composition comprising a mixture of a ketone/or an aldehyde and an alcohol in the presence of a catalyst according to claim 9 in a process for the enantioselective hydrogenation of beta-ketoesters,
and **without taking into account the presence of an acidic material.**

Re Item V.

1. The following documents are referred to in this communication:

- D1: RATOVELOMANANA-VIDAL, ADV. SYNTH. CATAL., vol. 345, 21.01.2003, pages 261-274
- D2: KING, J.ORG.CHEM., vol. 57, 1992, pages 6689-6691
- D3: KITAMURA, TETRAH. LETT., vol. 29, no. 13, 1988, pages 1555-1556
- D4: GENET, TETRAH.ASYMMETRY, vol. 5, no. 4, 1994, pages 675-690
- D5: ZHOU, J.A.C.S., vol. 124, (2002-03-08), pages 4952-4953

2. Clarity

2.1 Present claim 1 relates to a catalytic composition comprising a catalyst, an acidic

material and a buffering composition. According to claim 4 the acidic material comprises 'a substrate for asymmetric hydrogenation'. That means that the catalytic composition of claim 1 comprises one of the reactants, which is in contradiction with the general knowledge that a catalyst does not take part in a reaction and therefore, claim 1 lacks clarity within the meaning of Article 6 PCT.

Furthermore, the presence of an acidic material in the catalytic compositions is not supported by the description (Art. 5 PCT) since neither a definition of what is to be understood by 'acidic material', nor examples for the preparation of such compositions are present in the application's documents.

2.2 Lack of clarity also arises for present claim 8 which relates to a hydrogenation process comprising contacting the substrate with hydrogen and a catalyst, in the presence of an acidic material and a buffering composition. According to claim 11, the acidic material comprises 'a substrate suitable for asymmetric hydrogenation' and therefore, claim 8 lacks clarity within the meaning of Article 6 PCT.

2.3 Present independent claims 1, 8 and 15 further do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined because the claims attempt to define the subject-matter in terms of the result to be achieved (due to the expressions "catalyst effective for catalysing", "acidic material effective for activating the catalyst", "under condition effective for enantioselective hydrogenation", "in the presence of an effective catalyst", "acidic material for effecting such activation") which merely amounts to a statement of the underlying problem.

3. Novelty

D1-D3 concern the enantioselective hydrogenation of beta-keto esters in the presence of catalysts based on BINAP or other diphosphine-containing ligands.

D4 and **D5** concern the developing of new phosphine chiral ligands capable of high enantioselectivity in the hydrogenation of beta-keto esters.

None of the prior art documents cited in the International search report disclose catalytic

compositions comprising a) a mixture of a ketone(or aldehyde) and an alcohol as buffer and b) catalysts based on BINAP or other diphosphine-containing ligands.

The subject-matter of claims 1-15 restricted as above (see point III) can be considered to meet the requirements of Art. 33 (1) and (2) PCT.

4. Inventive Step

D1-D3, regarded as the most relevant prior art, concern the enantioselective hydrogenation of beta-keto esters in the presence of catalysts based on BINAP or other diphosphine-containing ligands and methods for the increasing of the enantiomeric excess. **D1** (see page 263, first paragraph) discloses that the use as solvent of the alcohol corresponding to the ketoester allows an increasing in the enantiomeric excess of the hydrogenation product (Table 3, ee%>99). In **D2**, such an increasing is observed by the addition of a very low level of a strong acid (ee%>97). **D3** shows the same effect by high-temperature, short-period reactions (ee%>97).

The subject-matter of the application differs from D1-D3 in the use of a buffer composition comprising of a mixture of a ketone(or aldehyde) and an alcohol in the reaction medium:

The technical problem to be solved can be regarded as the provision of a further process for the increasing of the enantiomeric excess in an asymmetric hydrogenation process of beta-ketoesters.

In view of the comparative examples of the application it is credible that this problem has actually been solved by mixing the substrate (i.e. the ketoester) with a buffering composition consisting of a mixture of ketone (or aldehyde) and alcohol before contacting it with the catalyst and hydrogen.

Since such a solution of the technical problem is neither disclosed, nor suggested in the prior art, the subject-matter of the application restricted as above and taking into account the clarity objections could be considered to meets the requirements of Article 33(3) PCT.

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(SEPARATE SHEET)**

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Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-03 097581 = D6	27.11.2003	21.05.2003	22.05.2002
WO-A-03 097569 = D7	27.11.2003	21.05.2003	22.05.2002

Documents D6 and D7 may constitute prior art in the national/regional phase of the present international application.